Cancel Claim 53.

54. The recombinant adenovirus of Claim 46 in which the region of the E4 early gene region which is deleted or mutated is open reading frame 6.

Cancel Claim 55.

Please add Claims 56 and 57 as follows:

--(new) 56. The recombinant adenoviral vector of Claim 46 or 47 which further comprises a deletion of the E3 gene region.

(new) 57. The packaging cell line of Claim 48, ~~49, or 50~~ which supports the growth of the recombinant ~~adenoviral vector~~ adenovirus which further comprises a deletion of the E3 gene region.--

REMARKS

Attorneys for Applicant note with appreciation that the Examiner has indicated Claims 37, 38, 40-45 and 52 are in condition for allowance.

The claims have been amended as suggested by the Examiner to more particularly point out and distinctly claim the invention. Applicants believe all the claims to be in condition for allowance.

1. The Rejections Under 35 U.S.C. § 112. First Paragraph, Should be Withdrawn

The specification is objected to and Claims 38-39, 46, 48-50, 54-55 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement.

Claims 38 and 48-50 are rejected under 35 U.S.C. § 112, first paragraph, for failure to provide an enabling disclosure. In particular, the Examiner contends that the specification is only enabling for the claimed invention wherein the recited packaging cell line is a 293-derived cell line. Claims 38 and 48-50 have been amended as suggested by the Examiner to recite a packaging cell line derived from a 293-derived cell line. The amendment of the claims is for the purpose of expediting allowance of the claims and is not to be viewed as an acquiescence of the Examiner's rejection. Applicants reserve the right to pursue claims to a non-293 derived packaging cell line in later filed applications. The claims as amended obviate the Examiner's rejection and thus, the rejection should be withdrawn.

Claims 46, 48, 49, 53 and 54 are rejected under 35 U.S.C. § 112, first paragraph, for failing to provide an enabling disclosure. In particular, the Examiner asserts that the specification fails to enable the recited recombinant adenoviral vector deficient in E1 and E4 early gene regions in addition to the E2A early gene region and a packaging cell line which supports replication of a recombinant adenovirus deleted of the E1 early region gene, E4 early region gene, and in addition the E2A gene region. The Examiner's rejection is in error and should be withdrawn.

The specification describes adenoviral vectors which contain deletions of the E1 and E4 early region genes, in addition to the E2A gene region. The specification also describes novel adenoviral packaging cell lines to complement the E1, E4 and E2A gene regions deleted from the recombinant adenoviruses of the present invention. Plasmids containing the E4 and E2A gene regions under the control of inducible promoters may be introduced into 293 cells, so that in an uninduced state expression of these cytotoxic genes is low enough to avoid toxicity to the host cell, but in an induced state is sufficiently activated to produce enough E4 and E2A to complement the replication-defective adenoviral vectors of the present invention. For example, see page 24, lines 5 to 27 of the instant application which describes the construction of a plasmid which contains the cytotoxic adenoviral E4 early gene region, deleted of its promoter, and placed under the control of an inducible mouse α inhibin promoter.

The Examiner's attention is invited to the accompanying Rule 132 declaration by Dr. Qing Wang (the "Wang declaration"), which describes the construction of a 293-derived packaging cell line which contains the cytotoxic gene regions, E4 and E2A, under the control of an inducible promoter, the mouse α-inhibin promoter. This cell line, designated 293-ORF6/E2A, has been constructed using the methods described in the instant application. The Wang declaration describes the construction of plasmids which provide the minimal essential region of E4 early region gene, open reading frame 6 (ORF 6) and the E2A gene region under control of an inducible promoter. The plasmids were

introduced into a 293 cell line, which expresses the E1 early gene region. The successful introduction of the two cytotoxic gene regions into 293 cells, in addition to the E1 early gene region already present, is demonstrated by Southern blot analysis (see ¶6 of the Wang declaration). The ability of such a cell line to grow and survive is demonstrated by the observations that the positively identified cell lines may be maintained for at least 12 tissue culture passage. The engineered cell line, 293-ORF6/E2A demonstrated similar growth characteristics to the 293 cell line engineered to express the E2A gene region, in addition to the E1 early gene region (see ¶7 of the Wang declaration). These results and observations demonstrate that a 293 cell expressing the E1 early gene region, in addition to E4-ORF6 and E2A under the control of an inducible promoter, may not only be successfully constructed, but may also be successfully grown and maintained in culture. The Wang declaration further demonstrates the 293-ORF6/E2A cell line may be constructed based on the disclosure of the above-identified application and that undue experimentation is not required by one skilled in the art to practice the invention as claimed. Therefore, the specification is fully enabling and the Examiner's rejection should be withdrawn.

Claims 39, 48-50 and 55 are rejected under 35 U.S.C. § 112, first paragraph, and the specification is objected to for failing to provide an enabling disclosure. In particular, the Examiner believes the specification to only be enabling for a packaging cell line in which the nucleic acid sequence which supplies the function of the E4 early region is linked to an inducible promoter.

Applicant's assert that the Examiner's rejection is based on an erroneous interpretation of the instant specification and the claims as amended. This application relates, in part, to a packaging cell line which supplies the cytotoxic adenoviral gene regions required for viral replication under the control of an inducible promoter, so that in an uninduced state the cytotoxic gene regions are expressed at low levels to avoid toxicity to the host cell, but in an induced state is sufficiently activated to make enough E4 and E2A to complement the deletions in the recombinant adenoviral vectors. In particular, Claim 39 is drawn to a 293-derived packaging cell line that supplies the function of the E4 early gene region operably linked to an inducible promoter; claims 48-50 are drawn to a 293-derived packaging cell line that supplies the function of the E4 early region operably linked to an inducible promoter. Therefore, the scope of the claims is fully supported by the instant application and the Examiner's rejections under § 112 should be withdrawn.

Claims 51 and 53 are rejected under 35 U.S.C. § 112, first paragraph, for failing to provide an enabling disclosure. Claims 51 and 53 have been canceled, thereby obviating the Examiner's rejection. The Examiner's rejections under 35 § 112 should be withdrawn.

2. The Rejections Under 35 U.S.C. § 112, Second Paragraph, Should be Withdrawn

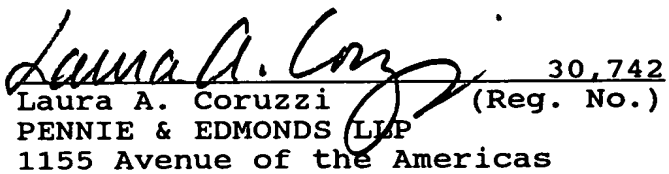
Claims 46-50 and 53-55 are rejected under 35 U.S.C.§ 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. Claims 46-50 have been amended to more particularly point out the invention as claimed, thereby obviating the Examiner's rejection. The Examiner's rejections under 35 U.S.C. § 112, should be withdrawn.

CONCLUSION

Applicants respectfully request entry and consideration of the foregoing amendments and remarks. Applicants believe the claims to be in condition for allowance.

Respectfully submitted,

Date November 12, 1997



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(Reg. No.)

Laura A. Coruzzi
PENNIE & EDMONDS LLP
1155 Avenue of the Americas
New York, New York 10036-2711
(212) 790-9090

Enclosure